the context of a prospective trial, we cannot exclude the possibility of multiple vaccine interactions; however, it appears unlikely at this time.

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A Simple, Inexpensive, Rapid, and Accurate Preclinical Model for In-Stent Restenosis

With great interest we read the recent review by Schwartz et al. (1) regarding preclinical animal restenosis models. Detailed descriptions of the current available animal restenosis models, the pathophysiology of in-stent restenosis (ISR), and the usefulness of animal restenosis models to predict clinical outcomes are presented. In the final remarks it is concluded that preclinical models are important but imperfect standards. A simple, inexpensive, rapid, and accurate preclinical model would be useful. However, in their description of available restenosis models, Schwartz et al. (1) overlooked two important and recently developed animal models of ISR. In these models, stents are implanted in the carotid artery (2) or in the abdominal aorta (3) of the rat. Pathophysiological processes of neoinitmal formation, such as thrombus formation, inflammation, and smooth muscle cell proliferation, evolve in an identical manner as seen in the rabbit iliac and pig coronary artery models. Moreover, in the rat abdominal aorta model, a positive correlation is found between the mean injury score and the neointimal area (2,3).

Rat ISR models enable thorough pathophysiological studies, as many antibodies to cellular proteins are available in the rat as compared to rabbits and pigs. By elucidation of the pathophysiology of ISR, more purposeful experiments to prevent ISR can be carried out. Rat models of ISR could provide important indications for the development of new anti-restenotic strategies (3). Generally, rat studies are preferable over rabbit or pig studies; only mainstream surgical equipment is required, animal facilities have large housing capacity for rats, and the costs for purchase are low.

Discrepancies between efficacy of anti-restenotic agents in preclinical and clinical studies have caused skepticism about the rat carotid artery model. For rat stent models this skepticism should be tempered, because differences in pathophysiological mechanisms between neointimal formation after balloon dilation alone and stent implantation are evident. Furthermore, rapamycin-eluting stents have been shown to inhibit neointimal formation in the rat abdominal aorta, a clear relation between preclinical and clinical outcomes in this model (3). In addition, these rat models enable stent research in transgenic diabetic and hypertensive strains. This offers a truer reflection of clinical settings in preclinical experiments, and might result in a better prediction of efficacy of anti-restenotic agents in clinical trials (2,3).

In conclusion, rat models are simple, inexpensive, rapid, and accurate preclinical models for ISR.

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REPLY

We read with interest the comments of Dr. Langeveld and colleagues concerning our recent review of preclinical restenosis models (1). These investigators write that stenting the rat carotid or abdominal artery provides a "simple, inexpensive, rapid, and accurate preclinical model for in-stent restenosis." We have several comments in response regarding the utility of the rat model.

A useful in-stent restenosis animal model should accurately predict: 1) safety, 2) efficacy, and 3) pathophysiologic mechanisms. These are addressed as follows.

Safety. The major safety issues for stents are thrombosis (acute or subacute) and neointimal thickening causing luminal stenosis. Although the rat model sometimes induces stent thrombosis, it does so to a lesser extent than the porcine and rabbit models. Total occlusion and severe stent stenosis do not generally occur in the rat model.

Efficacy. Rat carotid restenosis models were abandoned years ago because virtually all therapies that were tested and effective in rats later proved ineffective in patients. Such studies included

angiotensin-converting enzyme inhibition, heparin, and other anticoagulants, antiplatelet therapies, and corticosteroids. Much expense, time, and energy-conducting clinical trials were expended based on inaccurate results from rat models. This may occur as stent efficacy is determined by neointimal inhibition and prevention of negative remodeling. Rat vessels may develop enough neointima to cause arterial narrowing following stenting, but they do not appear to exhibit remodeling. Rat models of diabetes and hypertension exist that could theoretically test different aspects of human disease. Drug-eluting stents have been deployed in rat carotid arteries, and we are awaiting the outcome of these studies (R. Virmani, unpublished data, August 2005). Much current effort is directed toward establishing efficacy parameters in the pig and rabbit model, with promising early results by investigators such as Touchard et al. (personal communication, November 2005) or Finn et al. (personal communication, September 2005).

Simplicity, expense, rapidity. Stenting rat carotid arteries is as simple as stenting porcine or rabbit vessels. Whether the rat model is truly cheaper than the rabbit or porcine model is unclear. The purchase costs and per diem housing are higher with pigs than with rabbits or rats. This is partially overcome though by the ability to place three or sometimes four stents in a single pig, and two in the rabbit carotid or three to four stents in the rabbit aorta.

The porcine model offers the advantage of being an excellent coronary artery model for testing stent, guidewire, and catheter performance in arterial beds with size, shape, curvature, and tortuosity similar to humans. Flow dynamics in a small, noncoronary vessel such as in the rat differ dramatically from patients, with different shear and boundary layer flow. These may be important in the era of drug-eluting stents where elution is dependent on flow parameters. Elution studies have been performed in the rabbit iliac arteries and are similar to those in the pig (A. Finn, personal communication, September 2005).

Importantly, the major costs of preclinical restenosis studies relate to surgical time, histopathologic stent processing (requiring plastic embedding), and careful histomorphometric measurement. Using a rat model for this step is thus no simpler, and it saves neither time nor expense compared to rabbits or pigs.

Finally, it is certainly true that the available antibodies and knowledge of proteins and genes are greater for rats and mice compared to rabbits and pigs. However, given the desire by the interventionalist and the Food and Drug Administration to achieve parallel clinical trial results, elucidation of vascular response mechanisms in rodents may have limited translational value, although of scientific merit and interest.

Until stented rat models are validated against clinical trials for providing accurate results, we are hesitant to recommend this strategy, and we must continue to question scientifically the wisdom of their use in translational vascular research. Hence, large animal models continue to be the standard. In the meantime, vigorous scientific debate and discussion about animal models in vascular biology is both welcomed and exciting. There is no doubt that for safety studies we are limited to the pig coronary artery model, which also assesses the distal myocardial bed for ischemia and emboli.

Thus, we look forward to future scientific and validation studies of the stented rat model by Dr. Langeveld and others, and we thank them for their comments.

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